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EXAMINER	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,374	SU, XING	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-36* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 5/22/2006. Currently, Claims 1-17, 19-36 are pending. Claim 18 is canceled. Claims 19-21 are withdrawn from consideration.

2. The following rejections are either newly applied, or newly applied as necessitated by amendment, or are reiterated. Response to arguments follows. Specifically, the 103(a) rejection of Claims 33-36 as unpatentable over Mirkin et al. in view of Vo-Dinh et al. is newly applied.

3. This action is Nonfinal.

Withdrawn Objections

4. The objection to the abstract made in Section 9 of the previous office action, is moot in view of the amended abstract.

5. The objection to the specification made in Section 10 of the previous office action, is moot in view of the amended specification.

6. The objection to Claim 5 made in Section 11 of the previous office action, is moot in view of the amended claim.

7. The rejection of Claim 36 made in Section 5 of the previous office action is withdrawn. The rejection of Claim 36 is withdrawn because the claim language of "consists of pyrimidine residues" limits the nucleic acid to only pyrimidine residues. Vo-Dinh does not teach sequences composed of only pyrimidine residues.

New Grounds and New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112 Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-17, 32, 33-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-17 and 33-36 are rejected because Claim 1 and 33 recite the limitation "about 1 to 25 carbon atoms". The specification teaches carbon atoms of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 (paragraph 26). Though the specification does describe 1 to 25 carbon atoms, it does not describe "about 1" carbon atom.

Claim 3 is rejection because it recites the limitation "less than about 5" purine residues. The specification teaches less than 5, 4, 3, 2, but not "about 5" (Paragraph 24). "About 5" can be larger than 5.

Claim 32 is rejected because it recites the limitation "about 10 mV to about 100 mV" and "about 1 Hz to about 1MHz". The specification teaches that the current applied is 10-100mV and 1Hz to 1MHz (paragraph 102). The specification does not teach "about 10 mV" or "about 1 Hz". These ranges can be higher than the 10-100mV and 1Hz to 1MHz, which is taught by the specification.

Claim 34 is rejection because it recites the limitation "5 or fewer" purine residues. The specification teaches less than 5, 4, 3, 2, but not 5 purine residues (Paragraph 24).

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "less than about 5 purine residues". It is unclear with regard to the limitation of the number of purine residues which are claimed because "about 5" can be interpreted to mean purine residues larger than 5.

The term "weak" in claim 35 is a relative term which renders the claim indefinite. The term "weak" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Claim 35 recites the limitation "the positively-charged enhancer" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is suggested that "the" be replaced with "a" to put the claims into proper antecedent basis.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 5-7, 9-10, 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Nelson et al. (Lehniger Principles of Biochemistry 2000 New York).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Claim 16) (Abstract). With regard to Claim 1 and 15, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column). Cao et al. teaches the probes were connected to nanoparticle probes with 10 adenosine units (Figure 2). Nelson et al. teaches adensine comprises an amine group and a carbon atom (figure 3-5 and figure 10-4). Therefore the limitation of the probe being attached to a primary amine having an alkyl chain of about 1 to 25 carbon atoms is encompassed by the teaching of Cao et al. wherein the nanoparticle is connected to the probe with 10 adenosine units.

With regard to Claim 5, Cao et al. teaches the use of an AU nanoparticle modified with Cy3-labeled, alkylthiol-capped oligonucleotide strands as probes. These probes would be a composite of organic-inorganic nanoparticles.

With regard to Claims 6 and 7, Cao et al. teaches a method of determining the nucleotide position at of a SNP in a bound target sequence (p. 1539 Figure 4). With regard to Claim 9, Cao et al. teaches a method in which the target sequence is less than the combined length of the capture probe and the Raman-active probe (p. 1539 Figure 4). With regard to Claim 10, the claim is broadly interpreted to define the length of the Raman-active oligonucleotide probe as the "entire" probe length. Cao et al. teaches the probe is comprised of 110 oligonucleotide strands on an Au nanoparticle (p. 1537 2nd paragraph 1st column). It is inherent in the teaching that the combined length of the 110 oligonucleotide strands would be greater than the target probe length.

With regard to Claim 13, the methods of Cao et al. are conducted in the absence of an amplification step.

With regard to Claim 14, Cao et al. teaches a method in which each spot on the microarray is a target: capture probe duplex (abstract). Cao et al. teaches that at least one Raman dye label can be used as a probe, therefore Cao et al. teaches the limitation of 1000 or less molecules of Raman-active probes detected (p. 1537 Figure 1).

With regard to Claim 17, Cao et al. teaches a method of labeling nanoparticles with 6 different dyes and contacting each of the Raman probes to a different probe:target duplex on the array (p. 1538 Figure 2).

Response to Arguments

The response traverses the rejection. The response asserts that Cao et al. does not teach the use of a primary amine as an enhancer for detecting a Raman signal (p. 11 1st paragraph). This argument has been thoroughly reviewed but is not found persuasive because the claims are not drawn to a primary amine as an enhancer, but merely is drawn to a Raman active probe attached to an amine group with 1 to 25 carbons. Cao et al. teaches that the nanoparticle attached probe (Raman active probe) is joined to the nanoparticle using adenosine. Adenosine has an amine group and has carbon chain of 1 to 25 carbons, therefore Cao et al. teaches all the limitations of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 22-25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) in view of Van den Engh (US Patent 6133044 October 17 2000).

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to

Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). Bruchez Jr. et al. teaches the samples were read on a flow cytometer (p. 22 paragraph 310). Bruchez Jr. et al. teaches that mismatches could be distinguished using the flow cytometer (p. 22 paragraph 310). Therefore Bruchez et al. teaches a method in which the flow cytometer is applied and the differences between the first and second probe can be detected (in other words, mismatches can be detected). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

With regard to Claim 29, Bruchez, Jr. et al. teaches the method can be used in minisequencing methods, detecting mutations (nucleotide occurrences) (p. 3 paragraph 39). Bruchez, Jr. et al. teaches SNPs can be detected (p. 3 paragraph 39). Bruchez, Jr. et al. teaches the method for SNP detection can be multiplexed (p. 3 paragraph 41). Bruchez, Jr. et al. teaches one or more different populations can be blended together so that more than one population can be assayed at the same time (p. 3 paragraph 42). Bruchez, Jr. et al. teaches a multiplex methods in which different probe polynucleotides can be used simultaneously with corresponding different target polynucleotides (p. 3 paragraph 43).

Bruchez Jr. et al. teaches a method which using a flow cytometer to detect differences, however, Bruchez Jr. et al. does not teach that the flow cytometer applies a AC current.

Van den Engh teaches a method of using a high speed flow cytometer droplet system (Abstract). With regard to Claim 22, Van den Engh teaches to create oscillations the crystal is powered through an alternating voltage source (e.g. AC) (Column 9 lines 12-16).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez Jr. et al. to use in the method of processing samples using the flow cytometer droplet system as taught by Van den Engh. The ordinary artisan would want to modify the method of Bruchez Jr. which teaches the use of a flow cytometer to use the flow cytometer droplet system as taught by Van den Engh, because Van den Engh teaches that this system allows high speed processing without the need for high oscillator drive powers (abstract). Van den Engh teaches that the flow cytometer droplet system increases performance of the droplet flow cytometer in a low powered system with high processing rates (Column 3, lines 38-40, 57-59). The ordinary artisan would want to use a flow cytometer, which had a high processing rate in order to be able to determine nucleotide occurrences in samples quickly.

Response to Arguments

The response traverses the rejection. The response asserts that Bruchez Jr et al. does not teach an AC current (p. 12 1st full paragraph). This argument has been thoroughly reviewed but is not found persuasive because although Bruchez Jr. et al. does not teach the limitation of an AC current, Bruchez Jr. et al. does teach using a flow cytometer to distinguish mismatches. Bruchez Jr. et al. is silent with regard to if the flow cytometer uses AC current. Van den Engh, however, teaches a flow cytometer system which specifically uses AC current. It is prima facie obvious to use the flow cytometer system as taught by Van den Engh in the method of Bruchez Jr. because Van den Engh teaches the system produces a high processing rate which would allow the ordinary user to process samples quickly.

12. Claims 33-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh (US Patent 6,174,677 January 16, 2001) in view of Isola et al. (Analytical Chemistry 1998 Vol. 70 p. 1352).

Vo-Dinh teaches a method of using SER (surface enhanced Raman)-labeled gene probes for hybridization, detection, and identification of SER-labeled hybridized target oligonucleotides (Abstract). With regard to Claim 33, Vo-Dinh teaches that SER labels are bound to different target oligonucleotide strands (Column 9, lines 27-61). Vo-Dinh teaches using a Raman spectrometer to determine signal detection of the labeled targets (Column 21 lines 58-60). Vo-Dinh teaches using a photomultiplier tube operated in the photon counting mode (irradiating the nucleic acid with light). Vo-Dinh et al.

teaches capture probe sequences were synthesized with a 5' amino linker to bind to a nylon membrane (Column 23 lines 35-40). With regard to claim 34, Vo-Dinh teaches the use of aminoacridine as a SER label (e.g. a positively-charged enhancer) (Column 9, lines 27-61).

Vo-Dinh teaches a method wherein the probe is attached to a 5' amino linker, but Vo-Dinh is silent with regard to the number of carbons.

Isola et al. teaches the same method of using SER labeled gene probes for hybridization, detection and identification of SER labeled hybridized target oligonucleotides from the gag gene (Abstract). Isola et al. teaches synthesizing capture probes with a 6-carbon 5' amino linker (p. 1354 2nd column Binding of the Capture probe sequence).

Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Vo-Dinh to use 6-carbon 5' amino linker as taught by Isola et al. The ordinary artisan would want to modify the method of Vo-Dinh which teaches a method using a 5' amino linker to incorporate the 6-carbon 5' amino linker taught by Isola et al. because Isola et al. teaches the 6-carbon 5' amino linker is necessary to anchor the capture probe to the solid support (p. 1354 2nd column Binding of the Capture probe sequence).

Response to Arguments

The response traverses the rejection. The response asserts that Vo-Dinh does not teach an amine having an alkyl chain of carbon atoms (p. 12 last paragraph). These arguments has been thoroughly reviewed but is not found persuasive.

Vo-Dinh teaches attaching a 5' amine linker to the capture probe. Though Vo-Dinh does not specifically teach the number of carbons on the linker, it is obvious to use the 6 carbon 5' amine linker taught by Isola et al. because Isola et al. teaches the 6-carbon 5' amino linker is necessary to anchor the capture probe to the solid support (p. 1354 2nd column Binding of the Capture probe sequence).

13. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Nelson et al. (Lehniger Principles of Biochemistry 2000 New York).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic

probe (p. 1537 1st column last sentence and 2nd column). Cao et al. teaches the probes were connected to nanoparticle probes with 10 adenosine units (Figure 2). Nelson et al. teaches adensine comprises an amine group and a carbon atom (figure 3-5 and figure 10-4). Therefore the limitation of the probe being attached to a primary amine having an alkyl chain of about 1 to 25 carbon atoms is encompassed by the teaching of Cao et al. wherein the nanoparticle is connected to the probe with 10 adenosine units. (Claim 1).

Cao et al., however, does not specifically mention other Raman probes, which could be used in the method of SNP sequencing.

Cao et al. teaches another method of determining if multiple dyes could be used in a multiplex method (p. 1538 1st column 1st full paragraph). With regard to Claims 2-4 Cao et al. teaches one of the Raman probes that can be used is Rhodamine (e.g. an anime).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of SNP sequencing of Cao et al. to further include the use of other dyes such as Rhodamine. The ordinary artisan would have been motivated to use various Raman probes because Cao et al. teaches different Raman dyes can be used to label different oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use various types of labels to be able to multiplex the reaction for the obvious improvement of testing more than one SNP at a time.

Response to Arguments

The response traverses the rejection. The response asserts that Cao et al. does not teach the use of a primary amine as an enhancer for detecting a Raman signal (p. 14 1st and 2nd paragraph). This argument has been thoroughly reviewed but is not found persuasive. The 103 rejection was made based the obviousness teaching that different Raman dyes can be used to label different oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use various types of labels to be able to multiplex the reaction for the obvious improvement of testing more than one SNP at a time. The response asserts that these labels are not amines. The claims have not be amended to reflect that the Raman signaling is enhanced by the use of a primary amine, merely that the probe is linked to an amine. The claims are not drawn to using the amine as an enhancer. Cao et al. teaches that the nanoparticle attached probe (Raman active probe) is joined to the nanoparticle using adenosine. Adenosine has an amine group and has carbon chain of 1 to 25 carbons, therefore Cao et al. teaches all the limitations of the claim.

14. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Nelson et al. (Lehniger Principles of Biochemistry 2000 New York) in view of Lane et al. (US Patent 5,770,365 June 23, 1998).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column). Cao et al. teaches the probes were connected to nanoparticle probes with 10 adenosine units (Figure 2). Nelson et al. teaches adensine comprises an amine group and a carbon atom (figure 3-5 and figure 10-4). Therefore the limitation of the probe being attached to a primary amine having an alkyl chain of about 1 to 25 carbon atoms is encompassed by the teaching of Cao et al. wherein the nanoparticle is connected to the probe with 10 adenosine units. (Claim 1).

Cao et al., however, does not teach a method in which the capture probe and the oligonucleotide probe are ligated.

Lane et al. teaches a method of using nucleic acid capture moieties to detect nucleic acid sequences (Column 4, lines 19-25). Lane et al. teaches a labeled probe complementary to a target-complementary region of the capture moiety that is immobilized on insoluble support (Column 11, lines 30-35). With regard to Claim 12,

Lane et al. teaches a method in which the detectable probe is ligated to the capture probe (a duplex-binding ligand binding site) (Figure 3).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to further include the use ligated probes as taught by Lane et al. The ordinary artisan would have been motivated to improve the method of Cao et al. because Lane et al. teaches that the ligation method can be used for the detection of nucleic acid sequences, which do not occur near the terminus of an intact target strand (Column 12, lines 15-20).

Response to Arguments

The response traverses the rejection. The response asserts that Cao et al. does not teach the use of a primary amine as an enhancer for detecting a Raman signal (p. 15 1st full paragraph). This argument has been thoroughly reviewed but is not found persuasive. The claims have not been amended to reflect that the Raman signaling is enhanced by the use of a primary amine, merely that the probe is linked to an amine. The claims are not drawn to using the amine as an enhancer. Cao et al. teaches that the nanoparticle attached probe (Raman active probe) is joined to the nanoparticle using adenosine. Adenosine has an amine group and has carbon chain of 1 to 25 carbons, therefore Cao et al. teaches all the limitations of the claim.

15. Claims 1, 5-11 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastinen et al. (Genome Research July 2000 Vol. 10(7) p. 1031) in

view of Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Nelson et al. (Lehniger Principles of Biochemistry 2000 New York).

Pastinen et al. teaches a method of genotyping by allele-specific primer extension on a microarray (abstract). With regard to Claim 1 and 15, Pastinen et al. teaches a method in which a primer (probe) is attached to a microarray (Figure 1). Pastinen et al. teaches that a target is bound to the primer in which there is a region of single-strand (Figure 1). Pastinen et al. teaches that label dNTPs are then used to extend the probe-target complex and detection via fluorescence can be made at the 3' end (figure 1). With regard to Claim 6 and 7, Pastinen et al. teaches a method of genotyping single nucleotide polymorphisms (SNPs) (a nucleotide occurrence) using an allele specific primer extension on a microarray (Abstract).

With regard to Claim 8, Pastinen et al. teaches that the array can be composed of a multiplex of mutations (p. 1033 1st column last sentence and second column 1st paragraph). Pastinen et al. teaches a multiplex method of PCR followed by genotyping on microarrays (p. 1033 2nd column 1st paragraph). Pastinen et al. teaches a microarray composed of PCR reactions each drawn to a mutation of a target sequence (p. 1033 2nd column 1st paragraph). If you are targeting occurrences of a nucleotide it is inherent that the targeting would be the detection of nucleotide occurrences of a target segment.

It is obvious in the teaching that an array can be composed of probes wherein each probe is used to determine the nucleotide of each adjacent basepair.

With regard to Claim 11, Pastinen et al. teaches genotyping in which using

primer extension a user can determine the sequence of the extended target (Abstract). Pastinen et al. teaches using a array of a multiplex of primers each specifically near a SNP area of detections (p. 1033 1st column last sentence and second column 1st paragraph). It is obvious in the teaching that a user can make an array composes of probes that when extended can detect nucleotides. After detection of the nucleotide from each primer extension the complete sequence of the target could be determining by aligning the nucleotides from each probe.

Pastinen et al., however, does not teach using Raman probes instead of labeled dNTPs to determine the sequence identity.

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS Raman probes (Claim 16) (Abstract). With regard to Claim 1 and 15, Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column). Cao et al. teaches the probes were connected to nanoparticle probes with 10 adenosine units (Figure 2). Nelson et al. teaches adensine comprises an amine group and a carbon atom (figure 3-5 and figure 10-4). Therefore the limitation of the probe being attached to a primary

amine having an alkyl chain of about 1 to 25 carbon atoms is encompassed by the teaching of Cao et al. wherein the nanoparticle is connected to the probe with 10 adenosine units.

With regard to Claim 5, Cao et al. teaches the use of an AU nanoparticle modified with Cy3-labeled, alkylthiol-capped oligonucleotide strands as probes. These probes would be a composite of organic-inorganic nanoparticles.

With regard to Claims 6 and 7, Cao et al. teaches a method of determining the nucleotide position at of a SNP in a bound target sequence (p. 1539 Figure 4).

With regard to Claim 9, Cao et al. teaches a method in which the target sequence is less than the combined length of the capture probe and the Raman-active probe (p. 1539 Figure 4). With regard to Claim 10, the claim is broadly interpreted to define the length of the Raman-active oligonucleotide probe as the "entire" probe length. Cao et al. teaches the probe is comprised of 110 oligonucleotide strands on an Au nanoparticle (p. 1537 2nd paragraph 1st column). It is inherent in the teaching that the combined length of the 110 oligonucleotide strands would be greater than the target probe length.

With regard to Claim 14, Cao et al. teaches a method in which each spot on the microarray is a target: capture probe duplex (abstract). Cao et al. teaches that at least one Raman dye label can be used as a probe, therefore Cao et al. teaches the limitation of 1000 or less molecules of Raman-active probes detected (p. 1537 Figure 1).

With regard to Claim 17, Cao et al. teaches a method of labeling nanoparticles with 6 different dyes and contacting each of the Raman probes to a different probe:target duplex on the array (p. 1538 Figure 2).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Pastinen et al. to further include the use of Raman probes as taught by Cao et al. The ordinary artisan would be motivated to improve the method of Pastinen et al. because Cao et al. teaches a method of using Raman probes which would allow multiplex sequencing. The ordinary artisan would want to use Raman probes because Cao et al. teaches that Raman dyes can be used to label different oligonucleotides to distinguish oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use many probes with a variety of dyes in order to provide for multiplexing that would allow for the detection of an increased number of SNPs simultaneously.

Response to Arguments

The response traverses the rejection. (A) The response asserts allele specific primers are directed to single nucleotides and therefore allele specific primers are not designed to detect multiple occurrences (p. 15 last sentence and p. 16 first paragraph). (B) The response asserts Cao et al. does not teach or suggest replacement of the allele specific primer with an oligonucleotide and an enhancer (p. 16 1st full paragraph). (C) The response asserts there is no suggestion for substitution of the enhancement solution of Cao et al. for a primary amine (p. 16 2nd to last paragraph). This argument

has been thoroughly reviewed but is not found persuasive. The claims have not been amended to reflect that the Raman signaling is enhanced by the use of a primary amine, merely that the probe is linked to an amine.

(A) Though allele specific primers do only detect one mutation, Pastein et al. teaches a multiplex of allele specific primers (p. 1033 2nd column 1st full paragraph and Figure 1). The claims are not drawn to detecting multiple occurrences with 1 probe, but with determine a series of occurrences on a target. Therefore Pastein et al. teaches determining multiple occurrences on the same target by multiplexing allele specific primers.

(B) The motivation to combine Pastein et al. with Cao et al. comes from the teaching of Cao et al. to use Raman probes to distinguish sequences. The ordinary artisan would want to use Raman probes because Cao et al. teaches that Raman dyes can be used to label different oligonucleotides to distinguish oligonucleotide sequences (p. 1537 1st column 1st paragraph). The ordinary artisan would be motivated to use many probes with a variety of dyes in order to provide for multiplexing that would allow for the detection of an increased number of SNPs simultaneously. Using Raman probes allows the ordinary artisan to multiplex a target and detect many occurrences at once.

(C) The claims are not drawn to using the amine as an enhancer. Cao et al. teaches that the nanoparticle attached probe (Raman active probe) is joined to the nanoparticle using adenosine. Adenosine has an amine group and has carbon chain of 1 to 25 carbons, therefore Cao et al. teaches all the limitations of the claim.

16. Claims 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cao et al. (Science August 2002 Vol 297 p. 1536) as evidenced by Nelson et al. (Lehniger Principles of Biochemistry 2000 New York) in view of Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) and Van den Engh (US Patent 6133044 October 17 2000).

Cao et al. teaches a multiplexed detection method of oligonucleotide targets bound to capture probes and detected using SERS (surface enhanced Raman) Raman probes (Abstract). Cao et al. teaches a three-component sandwich assay used in a microarray (e.g. biochip) format composed of nanoparticle probes (Raman probes) detecting a bound target:capture probe duplex (p. 1537 1st column top of last paragraph). Cao et al. teaches the target: capture probe duplex has an over hanging region of the target sequences (single-stranded region) (p. 1537 1st column top of last paragraph). Cao et al. teaches that for each spot on the microarray a signal from the SER probe was measured using a Raman spectrometer coupled with a fiber-optic probe (p. 1537 1st column last sentence and 2nd column). Cao et al. teaches the probes were connected to nanoparticle probes with 10 adenosine units (Figure 2). Nelson et al. teaches adensine comprises an amine group and a carbon atom (figure 3-5 and figure 10-4). Therefore the limitation of the probe being attached to a primary amine having an alkyl chain of about 1 to 25 carbon atoms is encompassed by the teaching of Cao et al. wherein the nanoparticle is connected to the probe with 10 adenosine units. (Claim 1).

With regard to Claim 27, Cao et al. teaches a method that uses a multiple color scanning Raman method in which more than one label can make up each spot (p. 1538 2nd column). It is obvious to one skilled in the art that to determine the frequencies of each labeled used in the multiplex method one would need to look up the published spectra readings to determine which labels are incorporated in spot.

Cao et al., however, does not teach using probes that have a first and second signal attached nor using an AC current.

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). Bruchez Jr. et al. teaches the samples were read on a flow cytometer (p. 22 paragraph 310). Bruchez Jr. et al. teaches that mismatches could be distinguished using the flow cytometer (p. 22 paragraph 310). Therefore Bruchez et al. teaches a method in which the flow cytometer is applied and the differences between the first and second probe can be detected (in other words, mismatches can be detected). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

Van den Engh teaches a method of using a high speed flow cytometer droplet system (Abstract). With regard to Claim 22, Van den Engh teaches to create

oscillations the crystal is powered through an alternating voltage source (e.g. AC) (Column 9 lines 12-16).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Cao et al. to further include the use of Hairpin probes. The ordinary artisan would have been motivated to improve the method of Cao et al. because Bruchez et al. teaches a method particularly useful in multiplex settings where a plurality of different conjugates are used to assay for a plurality of different target polynucleotide and the large number of distinguishable semiconductor nanocrystal labels allows for simultaneous analysis of multiple labeled target polynucleotide (p. 2 paragraph 16). Therefore it would be prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez Jr. et al. to use in the method of processing samples using the flow cytometer droplet system as taught by Van den Engh. The ordinary artisan would want to modify the method of Bruchez Jr. which teaches the use of a flow cytometer to use the flow cytometer droplet system as taught by Van den Engh, because Van den Engh teaches that this system allows high speed processing without the need for high oscillator drive powers (abstract). Van den Engh teaches that the flow cytometer droplet system increases performance of the droplet flow cytometer in a low powered system with high processing rates (Column 3, lines 38-40, 57-59). The ordinary artisan would want to use a flow cytometer which had a high processing rate in order to be able to determine nucleotide occurrences in samples quickly.

Response to Arguments

The response traverses the rejection. (A) The response asserts that Cao et al. does not teach the use of a primary amine as an enhancer for detecting a Raman signal (p. 15 1st full paragraph). (B) The response asserts Bruchez, Jr. et al. does not teach a method of applying an alternating current (p. 17). These arguments have been thoroughly reviewed but are not found persuasive.

(A) The claims have not been amended to reflect that the Raman signaling is enhanced by the use of a primary amine, merely that the probe is linked to an amine. The claims are not drawn to using the amine as an enhancer. Cao et al. teaches that the nanoparticle attached probe (Raman active probe) is joined to the nanoparticle using adenosine. Adenosine has an amine group and has carbon chain of 1 to 25 carbons, therefore Cao et al. teaches all the limitations of the claim.

(B) Although Bruchez Jr. et al. does not teach the limitation of an AC current, Bruchez Jr. et al. does teach using a flow cytometer to distinguish mismatches. Bruchez Jr. et al. is silent with regard to if the flow cytometer uses AC current. Van den Engh, however, teaches a flow cytometer system which specifically uses AC current. It is prima facie obvious to use the flow cytometer system as taught by Van den Engh in the method of Bruchez Jr. because Van den Engh teaches the system produces a high processing rate which would allow the ordinary user to process samples quickly.

17. Claims 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) in view of Van den Engh (US Patent 6133044 October 17 2000) and Livak et al. (US Patent 5,723,591 March 3, 1998) as evidenced by DNA from Wikipedia.com.

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). Bruchez Jr. et al. teaches that mismatches could be distinguished using the flow cytometer (p. 22 paragraph 310). Therefore Bruchez et al. teaches a method in which the flow cytometer is applied and the differences between the first and second probe can be detected (in other words, mismatches can be detected). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

With regard to Claim 24 and 25, Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

Bruchez, Jr. et al., however, does not teach using an alternating current or the distance the quencher and reporter should be apart on the probe strand.

Van den Engh teaches a method of using a high speed flow cytometer droplet system (Abstract). With regard to Claim 22, Van den Engh teaches to create oscillations the crystal is powered through an alternating voltage source (e.g. AC) (Column 9 lines 12-16).

Livak et al. teaches that the quencher molecule and reporter should be between 6-16 nucleotides (Column 3, line 63). As evidenced by Wikepedia.com the distance between nucleotides is 0.23 nm, therefore the distance between a reporter and quencher can be between 1.38 to 3.68 nm apart (between 3-6 nm).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez, Jr. et al. to use in the method of processing samples the flow cytometer droplet system as taught by Van den Engh and to further include distance limitation as taught by Livak et al. The ordinary artisan would want to modify the method of Bruchez Jr. which teaches the use of a flow cytometer to use the flow cytometer droplet system as taught by Van den Engh, because Van den Engh teaches that this system allows high speed processing without the need for high oscillator drive powers (abstract). Van den Engh teaches that the flow cytometer droplet system increases performance of the droplet flow cytometer in a low powered system with high processing rates (Column 3, lines 38-40, 57-59). The ordinary artisan would want to use a flow cytometer which had a high processing rate in order to be able to determine nucleotide occurrences in samples quickly. The ordinary artisan would have been motivated to improve the method of Bruchez, Jr. et al. because Livak et al. teaches that there is a distance that must be maintained between the quencher and reporter in order for the quencher to be able to quench the reporter in the assay (Column 3, lines 60-65).

Response to Arguments

The response traverses the rejection. The response asserts Bruchez, Jr. et al. does not teach a method of applying an alternating current (p. 18). These arguments have been thoroughly reviewed but are not found persuasive. Although Bruchez Jr. et al. does not teach the limitation of an AC current, Bruchez Jr. et al. does teach using a flow cytometer to distinguish mismatches. Bruchez Jr. et al. is silent with regard to if the flow cytometer uses AC current. Van den Engh, however, teaches a flow cytometer system which specifically uses AC current. It is prima facie obvious to use the flow cytometer system as taught by Van den Engh in the method of Bruchez Jr. because Van den Engh teaches the system produces a high processing rate which would allow the ordinary user to process samples quickly.

18. Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchez, Jr. et al. (US Patent Application 09/815585 March 21, 2002) in view of Chan et al. (US Patent Application Publication March 27, 2003).

Bruchez, Jr. et al. teaches a method for assay a sample for a target oligonucleotide using semiconductor nanocrystals (Abstract and title). With regard to Claim 22, Bruchez, Jr. et al. teaches a hairpin probe attached to an encoded microsphere (Figure 2). Bruchez Jr. et al. teaches that mismatches could be distinguished using the flow cytometer (p. 22 paragraph 310). Therefore Bruchez et al. teaches a method in which the flow cytometer is applied and the differences between

the first and second probe can be detected (in other words, mismatches can be detected). With regard to Claim 23, Bruchez, Jr. et al. teaches that the molecular beacon hairpin probe (two labels on the probe) in the presence of target DNA will bind to the target DNA and a fluorescent signal will be detected (Figure 2 and 3).

Bruchez, Jr. et al. teaches that the flurophores, which can be used as labels, include TAMRA and ROX (p. 13 paragraph 151).

With regard to Claim 29, Bruchez, Jr. et al. teaches the method can be used in minisequencing methods (p. 3 paragraph 39). A minisequencing method would be used to determine the nucleotide at each position of a target sequence using a population of probes.

Bruchez, Jr. et al., however, does not teach using an alternating current or reading each nucleotide as it passes through a channel optically.

Chan et al. teaches a method for spatial resolution of signal detection (Abstract). With regard to Claim 30, Chan et al. teaches a method of passing a target through an optical detector to read florescent signals (p. 12 paragraphs 114 and 115). With regard to Claim 31, Chan et al. teaches an interactor station comprised of the channel and the optical detector (e.g. a microelectromechical system) (p. 12 paragraph 115). With regard to Claim 32, Chan et al. teaches that the target nucleotide is pulled through the nanoslit of the channel by applying an alternating current (AC current) filed to the metal layer (p. 14 paragraph 132). Chan et al. teaches the optical system uses radiation

modulated frequencies (AC current oscillations) in the range of 10 MHz to 1 GHz (p. 15 paragraph 138).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bruchez Jr. et al. to further include the use of a channel, optical detector, and AC current as taught by Chan et al. The ordinary artisan would have been motivated to improve the method of Bruchez Jr. et al. to include the channel, optical detector, and AC current taught by Chan et al. because Chan et al. teaches a method of linear analysis of DNA which can allow for the development of specific sequences to be used in sequence-specific tagging (p. 1 paragraph 3 and 4).

Response to Arguments

The response traverses the rejection. The response asserts Bruchez Jr. et al. does not teach using alternating current prior to detection (p. 19). The response asserts Chan et al. does not teach using a current to move molecules prior to detection (p. 19). These arguments have been thoroughly reviewed but are not found persuasive. Although Bruchez Jr. et al. does not teach the limitation of an AC current, Bruchez Jr. et al. does teach using a flow cytometer to distinguish mismatches. The use of the flow cytometer is immediately prior to detection. The sample must go through the flow cytometer before detection is measured. Bruchez Jr. et al. does not teach using an AC current in the flow cytometer. Chan et al. does teach detecting using an AC current. The ordinary artisan would be motivated to use the AC current in the bio imagining device of Bruchez

Jr. because Chan et al teaches channel, optical detector, and AC current taught by Chan et al. because a method of linear analysis of DNA which can allow for the development of specific sequences to be used in sequence-specific tagging (p. 1 paragraph 3 and 4).

19. Claims 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al. (US Patent 6361944 March 26, 2002) in view of Vo-Dinh (US Patent 6,174,677 January 16, 2001).

With regard to Claim 33, Mirkin et al. teaches a method of detecting a nucleic acid (Abstract). Mirken et al. teaches attaching an Amino-modifier C7 CPG solid support (amine with 7 carbon linker) to the nucleic acid (Column 58 lines 42-44). Mirken et al. teaches nanoparticles can be gold or silver (Column 16 lines 30-31). Mirken et al. teaches a gold nanoparticle is added to the probe solution (Column 58 lines 66-67). Mirken et al. teaches that florescence was detected (Column 59 line 28). Mirkin et al. teaches the nucleic acid is attached to a nanoparticle and a detectable color change is brought about as a result of hybridization (Abstract). With regard to Claims 34 and 36, Mirkin et al. teaches the detection of a nucleic acid which consists only of pyrimidine residues (Seq ID No. 9 Figure 10). With regard to Claim 35, Mirken et al. teaches absorbance (signal) is reduced (weak) without a nanoparticle (positively-charged enhancer) (Figure 19A).

Mirkin et al., however, does not teach detecting a Raman signal.

Vo-Dinh teaches a method of using SER (surface enhanced Raman)-labeled gene probes for hybridization, detection, and identification of SER-labeled hybridized target oligonucleotides (Abstract). With regard to Claim 33, Vo-Dinh teaches using a Raman spectrometer to determine signal detection of the labeled targets (Column 21 lines 58-60). Vo-Dinh teaches using a photomultiplier tube operated in the photon counting mode (irradiating the nucleic acid with light). Vo-Dinh et al. teaches that to activate SER (to be able to detect Raman signals) the nanoparticle can be coated with a solution of silver or gold (Column 9, lines 13-15).

Therefore it would have been prime facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Mirken et al. detect nucleic acids by measuring Raman signal as taught by Vo-Dinh et al. The ordinary artisan would have been motivated to modify the method of Mirken et al. detect nucleic acids by measuring Raman signal as taught by Vo-Dinh et al., because Vo-Dinh et al. teaches SER technology is provides a highly multiplex approach due to the capability of detecting sharp Raman peaks (Column 6, lines 27-30). Vo-Dinh et al. teaches the main advantage of SERS is to detect a large number of distinct labeling molecules that generate very sharp peaks (Column 7 lines 12-15). Vo-Dinh et al. teaches the SERS detection technique offers multiplex capability and minimizes the time and expense of gene detection (Column 7, lines 18-21). The ordinary artisan would be motivated to use the gold labeled probes (SER active) of Mirken et al. in the SERS method taught by Vo-Dinh et al. to detect a large number of sequences while minimizing time and expense

but producing detection data in which differences in nucleotides can be detected (differences in sharp peaks).

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Katherine Salmon
Examiner
Art Unit 1634

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